



4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2020-N-1680]

International Drug Scheduling; Convention on Psychotropic Substances; Single Convention on Narcotic Drugs; Isotonitazene; MDMB-4en-PINACA; CUMYL-PEGACLONE; Flubromazolam; Clonazepam; Diclazepam; 3-MeO-PCP; DIPHENIDINE; 2-MEO-DIPHENIDINE; 5-MEO-DALT; and 3-FLUOROPHENMETRAZINE (3-FPM);

Request for Comments

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; request for comments.

SUMMARY: The Food and Drug Administration (FDA or the Agency) is requesting interested persons to submit comments concerning abuse potential, actual abuse, medical usefulness, trafficking, and impact of scheduling changes on availability for medical use of 11 drug substances. These comments will be considered in preparing a response from the United States to the World Health Organization (WHO) regarding the abuse liability and diversion of these drugs. WHO will use this information to consider whether to recommend that certain international restrictions be placed on these drug substances. This notice requesting comments is required by the Controlled Substances Act (CSA).

DATES: Submit either electronic or written comments by August 28, 2020.

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. Electronic comments must be submitted on or before August 28, 2020. The <https://www.regulations.gov> electronic filing system will accept comments until

11:59 p.m. Eastern Time at the end of August 28, 2020. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <https://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <https://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <https://www.regulations.gov>.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in “Instructions.”

Instructions: All submissions received must include the Docket No. FDA-2020-N-1680 for “International Drug Scheduling; Convention on Psychotropic Substances; Single Convention on Narcotic Drugs; Isotonitazene; MDMB-4en-PINACA; CUMYL-PEGACLONE; Flubromazepam; Clonazepam; Diclazepam; 3-MeO-PCP; DIPHENIDINE; 2-MEO-DIPHENIDINE; 5-MEO-DALT; and 3-FLUOROPHENMETRAZINE (3-FPM); Request for Comments.” Received comments, those filed in a timely manner (see ADDRESSES), will be placed in the docket and, except for those submitted as “Confidential Submissions,” publicly viewable at <https://www.regulations.gov> or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states “THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.” The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <https://www.regulations.gov>. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the

body of your comments and you must identify this information as “confidential.”

Any information marked as “confidential” will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA’s posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: <https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf>.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to <https://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the “Search” box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

FOR FURTHER INFORMATION CONTACT: James R. Hunter, Center for Drug Evaluation and Research, Controlled Substance Staff, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 5150, Silver Spring, MD 20993-0002, 301-796-3156, james.hunter@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background

The United States is a party to the 1971 Convention on Psychotropic Substances (Psychotropic Convention). Article 2 of the Psychotropic Convention provides that if a party to the convention or WHO has information about a substance, which in its opinion may require international control or change in such control, it shall so notify the Secretary-General of the United Nations (the U.N. Secretary-General) and provide the U.N. Secretary-General with information in support of its opinion.

Paragraph (d)(2)(A) of the CSA (21 U.S.C. 811) (Title II of the Comprehensive Drug Abuse Prevention and Control Act of 1970) provides that when WHO notifies the United States under Article 2 of the Psychotropic Convention that it has information that may justify adding a drug or other substances to one of the schedules of the Psychotropic Convention, transferring a drug or substance from one schedule to another, or deleting it from the schedules, the Secretary of State must transmit the notice to the Secretary of Health and Human Services (Secretary of HHS). The Secretary of HHS must then publish the notice in the *Federal Register* and provide opportunity for interested persons to submit comments that will be considered by HHS in its preparation of the scientific and medical evaluations of the drug or substance.

II. WHO Notification

The Secretary of HHS received the following notice from WHO (non-relevant text removed):

Ref.: C.L.22.2020

The World Health Organization (WHO) presents its compliments to Member States and Associate Members and in reference to C.L.14.2019 has the pleasure of informing that the 43rd Expert Committee on Drug Dependence (ECDD) will meet from 12 to 16 October 2020 in Geneva, Switzerland. In the event that the meeting should be held virtually due to exceptional circumstances, corresponding arrangements will be made. Given that ECDD meetings are of a closed nature, this letter serves to notify Member States of the substances under review at the 43rd ECDD, which are in the Annex I for reference.

WHO is mandated by the 1961 and 1971 International Drug Control Conventions to make recommendations to the UN Secretary-General on the need for and level of international control of psychoactive substances based on the advice of its independent scientific advisory body, the ECDD. To assess the appropriate control of a psychoactive substance, the ECDD convenes annually to review the potential of this substance to cause dependence, abuse and harm to health, as well as any therapeutic applications. In order to perform this review and make scientific and evidence-based decisions, the ECDD conducts medical, scientific, and public health evaluations of the selected psychoactive substances using the best available information.

Although the meetings are of a closed nature, Member States are invited to contribute to the ECDD review process by joining the 43rd ECDD Open Session on 12 October 2020. The Open Session will allow interested parties to present information concerning substances under review to the Expert Committee. Registration information will be made available on the ECDD website:
<https://www.who.int/medicines/access/controlled-substances/en/>.

As in the past and in line with the publication “*Guidance on the WHO review of psychoactive substances for international control*” (EB126/2010/REC1, Annex 6)¹, Member States can also contribute to the ECDD review process by providing accurate information concerning the substances under review in advance of the meeting. For this purpose, a questionnaire will be sent to Member States to gather country information on the legitimate use, harmful use, status of national control and potential impact of international control for each substance under evaluation.

In addition to the questionnaire, Member States are also encouraged to provide any additional relevant information (unpublished or published) on substances to be reviewed by the 43rd ECDD by emailing ecddsecretariat@who.int with the subject “Ref: C.L.22.2020”.

The World Health Organization takes this opportunity to renew to Member States and Associate Members the assurance of its highest consideration.

GENEVA, 23 June 2020

¹https://apps.who.int/gb/ebwha/pdf_files/EB126-REC1/B126_REC1-en.pdf#page=58.

Annex I

43rd Expert Committee on Drug Dependence (ECDD) 12 - 16 October 2020, Substances For Review

The substances listed below have never been formally reviewed by WHO and are not currently under international control. Information was brought to WHO’s attention that these substances are clandestinely manufactured, of especially serious risk to public health and society, and of no recognized therapeutic use by any Party.

Critical Review

Synthetic Opioids	1. Isotonitazene
Synthetic Cannabinoid Receptor Agonists	2. MDMB-4en-PINACA 3. CUMYL-PEGALONE
Benzodiazepines	4. Flubromazepam 5. Clonazepam 6. Diclazepam
Dissociative-type substances	7. 3-MeO-PCP 8. DIPHENIDINE 9. 2-MEO-DIPHENIDINE
Hallucinogen	10. 5-MEO-SALT
Synthetic Stimulant	11. 3-FLUOROPHENMETRAZINE (3-FPM)

FDA has verified the website addresses contained in the WHO notice, as of the date this document publishes in the *Federal Register*, but websites are subject to change over time. Access to view the WHO questionnaire can be found at <https://www.who.int/teams/health-product-and-policy-standards/controlled-substances/ecdd-member-state-questionnaire>.

III. Substances Under WHO Review

Isotonitazene (chemical name: *N,N*-diethyl-2-(2-(4 isopropoxybenzyl)-5-nitro-1*H*-benzimidazol-1-yl)ethan-1-amine) is a potent synthetic opioid that is abused similar to other synthetic opioids. Its use has resulted in adverse health effects, including positively identified in 49 death investigation cases in the United States between August 2019 and April 2020. Law enforcement data indicate that isotonitazene has appeared in the United States' illicit drug market. According to the National Forensic Laboratory Information System (NFLIS) database, there have been 53 encounters of isotonitazene in the United States (as of June 2020). There are no commercial or approved medical uses for isotonitazene. On June 18, 2020, the Drug Enforcement Administration issued a notice of intent to temporarily control isotonitazene as a schedule I substance under the CSA.

MDMB-4en-PINACA is a synthetic cannabinoid that has been sold online and used to mimic the biological effects of tetrahydrocannabinol (THC), the main psychoactive constituent in marijuana. Research and clinical reports have demonstrated that synthetic cannabinoids are applied onto plant material so that the material may be smoked as users attempt to obtain a euphoric and psychoactive “high”. Synthetic cannabinoids have been marketed under the guise of “herbal incense,” and promoted by drug traffickers as legal alternatives to marijuana. According to the NFLIS database, MDMB-4en-PINACA was first encountered in the United States in January 2019. There have been 1,436 encounters of MDMB-4en-PINACA in the United States (as of July 6, 2020). MDMB-4en-PINACA has also been encountered mixed with opioids including heroin and fentanyl, with some incidents resulting in violent behaviors, tachycardia, and hypertension. There are no commercial or approved medical uses for MDMB-4en-PINACA and MDMB-4en-PINACA is not a controlled substance under the CSA.

CUMYL-PEGACLONE is a synthetic cannabinoid that has been sold online and used to mimic the biological effects of THC, the main psychoactive constituent in marijuana. Research and clinical reports have demonstrated that synthetic cannabinoids are applied onto plant material so that the material may be smoked as users attempt to obtain a euphoric and psychoactive “high”. Synthetic cannabinoids have been marketed under the guise of “herbal incense,” and promoted by drug traffickers as legal alternatives to marijuana. In vitro studies demonstrate that CUMYL-PEGACLONE binds to and activates the cannabinoid one receptor. CUMYL-PEGACLONE has not been encountered within the United States according to the NFLIS database (as of July 6, 2020). There are no commercial or approved medical uses for CUMYL-PEGACLONE and is not a controlled substance under the CSA.

Flubromazolam, clonazepam, and diclazepam belong to a class of substances known as benzodiazepines. Benzodiazepines produce central nervous system depression and are commonly used to treat insomnia, anxiety, and seizure disorders. Flubromazolam is a triazole analogue of the designer benzodiazepine, flubromazepam. Flubromazolam can be purchased on the internet and is used as a recreational substance in the United States. Flubromazolam has been identified in an increasing number of law enforcement seizures and has been associated with an increasing number of drug overdose deaths. It is abused by a broad range of groups including youths, young adults, and older adults. Clonazepam has been involved in an increasing number of drug seizure events as well as drug overdose deaths, alone and in combination with alcohol. Diclazepam is a designer benzodiazepine sold on the internet and most often found as a liquid solution, but it may be sold as a powder, tablet, blotter paper, or pellet. In 2018, flubromazolam, clonazepam, and diclazepam were all identified by law enforcement in driving under the influence of drugs cases in the United States. Flubromazolam, clonazepam, and diclazepam are not approved for medical use in the United States and are not controlled substances under the CSA.

3-MeO-PCP (3-methoxyphencyclidine; chemical name: 1-(1-(3-methoxyphenyl)cyclohexyl)piperidine) is a novel N-methyl-D-aspartate (NMDA) receptor antagonist with structural and biochemical similarities to phencyclidine (PCP) and other arylcyclohexylamines. 3-MeO-PCP is classified as an arylcyclohexylamine and produces dissociative anesthetic and hallucinogenic effects. Use of this substance is associated with intoxication and published case reports of both fatal and non-fatal overdose. 3-MeO-PCP is encountered by law enforcement in drug seizure reports. 3-MeO-PCP is an analogue of the Schedule II hallucinogen PCP. There is no approved medical use for 3-MeO-PCP in the United

States. 3-MeO-PCP is not a controlled substance under the CSA. If intended for human consumption, 3-MeO-PCP may be treated as a “controlled substance analogue” under the CSA pursuant to 21 U.S.C 802(32) (A) and 813.

DIPHENIDINE (chemical name: 1-(1,2-diphenylethyl) piperidine) is a non-competitive NMDA receptor antagonist classified as a diarylethylamine and produces dissociative anesthetic and hallucinogenic effects. It was originally synthesized in the 1920s, but reports of abuse started in the last decade. Use of this substance is associated with intoxication and published case reports of both fatal and non-fatal overdose outside of the United States. DIPHENIDINE is encountered by law enforcement in drug seizure reports. DIPHENIDINE is not approved for medical use in the United States and is not a controlled substance under the CSA.

2-MeO-DIPHENIDINE (2-methoxy-diphenidine, methoxphenidine) is a non-competitive NMDA receptor antagonist classified as a diarylethylamine and produces dissociative anesthetic and hallucinogenic effects that may produce effects similar to high doses of dextromethorphan. Use of this substance is associated with intoxication and non-fatal overdose in published case reports outside the United States. 2-MeO-DIPHENIDINE is encountered by law enforcement in drug seizure reports. There is no approved medical use for 2-MeO-DIPHENIDINE in the United States and 2-MeO-DIPHENIDINE is not a controlled substance under the CSA.

5-MeO-DALT (chemical name: *N,N*-Diallyl-5-methoxytryptamine) is a tryptamine hallucinogen and is an agonist of the serotonin (5-HT) 5-HT_{2A} receptor. 5-MeO-DALT appears to produce hallucinogenic effects similar to other tryptamine hallucinogens and fully substituted for 2,5-dimethoxy-4-methylamphetamine (DOM) in DOM-trained rats. 5-MeO-DALT is an analogue of the Schedule I controlled substance 5-methoxy-*N,N*-diisopropyltryptamine (5-MeO-DiPT). 5-MeO-DALT has been encountered by law enforcement in drug seizure reports. 5-

MeO-DALT is not approved for medical use in the United States and is not controlled under the CSA.

3-FLUOROPHENMETRAZINE (3-FPM) (chemical name: 1-(3-fluorophenyl)-2-(methylamino)propan-1-one) shares substantial chemical structural similarity to phenmetrazine, a Schedule II controlled substance that was prescribed as an appetite suppressant before being withdrawn from the pharmaceutical drug market in the United States because of its abuse potential. 3-FPM, which is similar to phenmetrazine and other stimulant drugs of abuse, increases extracellular concentrations of the neurotransmitter dopamine by inhibiting the uptake of this neurotransmitter at the dopamine transporter. Elevated extracellular dopamine concentrations have been implicated in the mechanism of action of stimulant drugs of abuse. There is no approved medical use for 3-FPM in the United States and 3-FPM is not a controlled substance under the CSA.

IV. Opportunity to Submit Domestic Information

As required by paragraph (d)(2)(A) of the CSA, FDA, on behalf of HHS, invites interested persons to submit comments regarding the 11 drug substances. Any comments received will be considered by HHS when it prepares a scientific and medical evaluation for drug substances that is responsive to the WHO Questionnaire for these drug substances. HHS will forward such evaluation of these drug substances to WHO, for WHO's consideration in deciding whether to recommend international control/decontrol of any of these drug substances. Such control could limit, among other things, the manufacture and distribution (import/export) of these drug substances and could impose certain recordkeeping requirements on them.

Although FDA is, through this notice, requesting comments from interested persons, which will be considered by HHS when it prepares an evaluation of these drug substances, HHS

will not now make any recommendations to WHO regarding whether any of these drugs should be subjected to international controls. Instead, HHS will defer such consideration until WHO has made official recommendations to the Commission on Narcotic Drugs, which are expected to be made in late-2020. Any HHS position regarding international control of these drug substances will be preceded by another *Federal Register* notice soliciting public comments, as required by paragraph (d)(2)(B) of the CSA.

Dated: July 29, 2020.

Lowell J. Schiller,

Principal Associate Commissioner for Policy.

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